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Gene Section

Review

SLC6A4 (solute carrier family 6 member 4)

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Abstract

The SLC6A4 gene encodes a sodium-dependent serotonin reuptake protein delivering the neurotransmitter serotonin from the synaptic cleft back to the presynaptic end. Its main function is to abort the activity of serotonin and forward it to neurotransmitter pool for recycling. The psychomotor stimulant drugs mainly amphetamines and cocaine act on this transmembrane protein which is a member of the sodium: neurotransmitter symporter family. SLC6A4 gene polymorphisms affect the rate of serotonin reuptake and play an important role in pathogenesis of various illnesses like Sudden infant death syndrome, aggressive behaviour in Alzheimer patients, Seasonal affective disorder, Major depressive Disorder and Obsessive-compulsive disorder.

Keywords

Solute Carrier Family 6 Member 4 (SLC6A4), Serotonin (5-HT), Serotonin transporter protein (5-HTT), Anxiety, Alcoholism, Hypertension, Mental Disorders.

Identity

Other names: 5-HTT, 5-HTTLPR, 5HTT, HTT, OCD1, SERT, SERT1, hSERT

HGNC (Hugo): SLC6A4

Location: 17q11.2

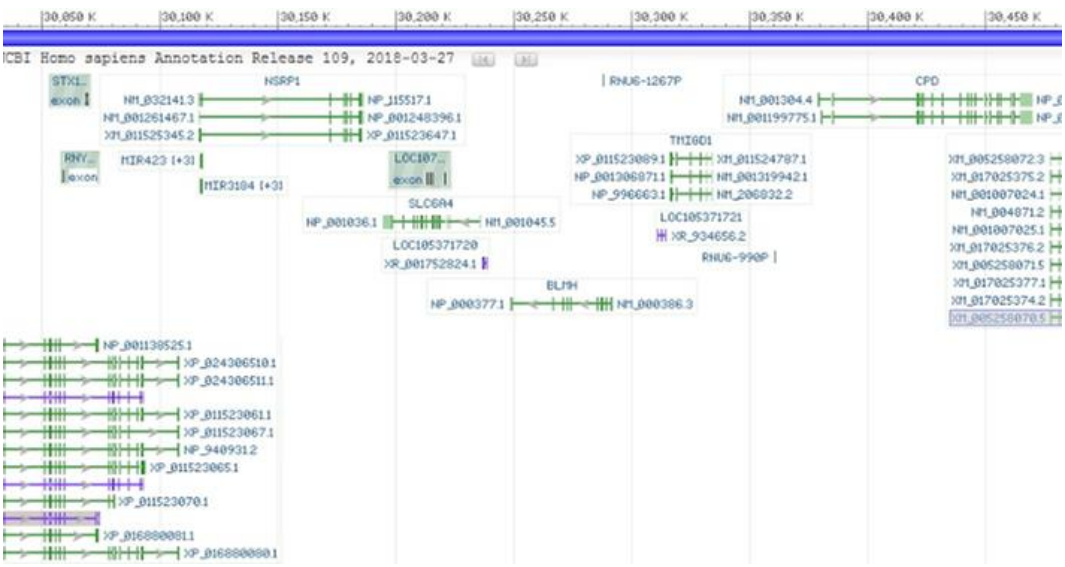

Figure 1. Genomic location of SLC6A4 (Chromosome 17 - NC_000017.11 Reference GRCh38.p12 Primary Assembly)

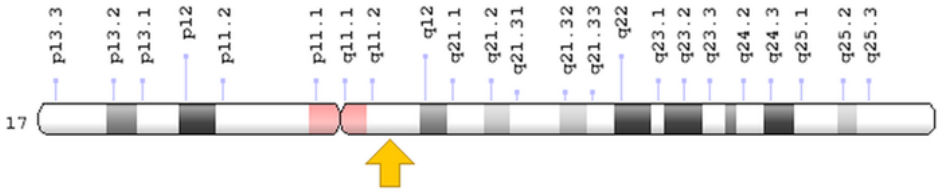

Figure 2. Chromosomal Location of SLC6A4. Cytogenetic Location: 17q11.2, which is the long (q) arm of chromosome 17 at position 11.2 (U.S. National Library of Medicine)

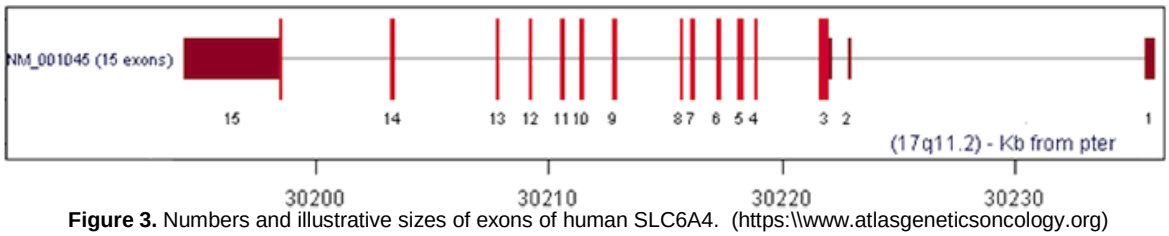

Figure 3. Numbers and illustrative sizes of exons of human SLC6A4. (https:\\www.atlasgeneticsoncology.org)

DNA/RNA

The SLC6A4 gene is 41,684 bp long (according to UCSC, GRCh38/hg38), located on the plus strand and spans 15 exons (NCBI Homo sapiens Annotation Release 109).

Transcription

The gene has 5 transcripts (Table 1)

Name	Transcript ID	bp	Protein (aa)	Biotype
SLC6A4-201	ENST00000261707.7	6604	630 aa	Protein coding
SLC6A4-202	ENST00000394821.2	2160	618 aa	Protein coding
SLC6A4-203	ENST00000401766.6	6543	630 aa	Protein coding
SLC6A4-204	ENST00000578609.1	566	No protein	Retained intron
SLC6A4-205	ENST00000579221.5	1069	72 aa	Nonsense mediated decay

Table 1. Transcripts of human SLC6A4 gene (Ensemble, GRCh38.p12).

Protein

SLC6A4 gene encodes a serotonin transporter protein (5-HTT) of 70,320 Dalton and composed of 630 amino acids (Figure 4) (Ramamoorthy et al., 1993). The protein belongs to family of neurotransmitter/sodium transporter (NSS). NSS family also includes dopamine, glycine and γ - aminobutyric acid (GABA) transporters (Chen et al., 2004). The members of this family have 12 transmembrane domains and intracellular N and C terminal regions (Yamashita et al., 2005). The large extracellular structure (EL) between TM3 and TM4 is modified by N-linked glycosylation in all eukaryotic NSS proteins and the number of N-linked glycosylation sites can vary from carrier to carrier. The consensus sequence for N-linked glycosylation is N-X-S/T (the amide nitrogen glycan binding region in the asparagine side chain and X is any amino acid except proline) (Mitra et al., 2006).

The EL2 of the 5-HTT protein has two glycosylation sites carrying glycan (Tate and Blakely,. 1994). Mutations in the glycosylation sites of 5-HTT and other NSS proteins generally cause problems in the transport of neurotransmitter proteins such as serotonin at the cell surface (Tate and Blakely,.1994 ; Olivares et al., 1995; Melikian et al., 1996; Li et al., 2004).

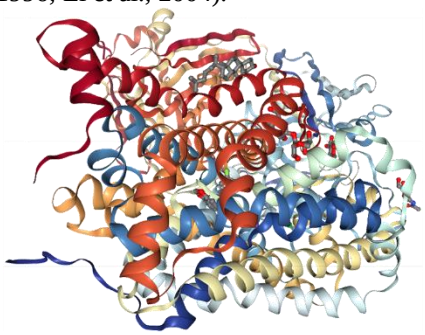

Figure 4. Structure of human Solute carrier family 6 member 4. X-ray structure of the ts3 human serotonin transporter complexed with paroxetine (selective serotonin re-uptake inhibitor) at the central site (PDB ID: 5I6X) (https://www.rcsb.org).

Expression

SLC6A4 gene is most commonly expressed in gastrointestinal tract, female tissues, and lung. It is less expressed in muscle, skin, endocrine, male, and female tissues (http://www.proteinatlas.org).

Localisation

SLC6A4 is found in various cellular compartments such as cytosol, endosome, plasma membrane, and integral component of plasma membrane, integral component of postsynaptic membrane, integral component of presynaptic membrane, endomembrane system, neuron projection, and serotonergic synapse (Müller et al., 2006; Brenner et

al., 2007; Ahmed et al., 2008; Ahmed et al., 2009; Gaudet et al., 2011).

Function

5-HTT protein activity relies on the concentrations of intracellular potassium and extracellular sodium and chloride ions. It also depends on the membrane potential generated by sodium-potassium adenosine triphosphatase for the activity of the 5-HTT protein. The 5-HTT protein binds itself to sodium, serotonin and chloride ions, respectively.

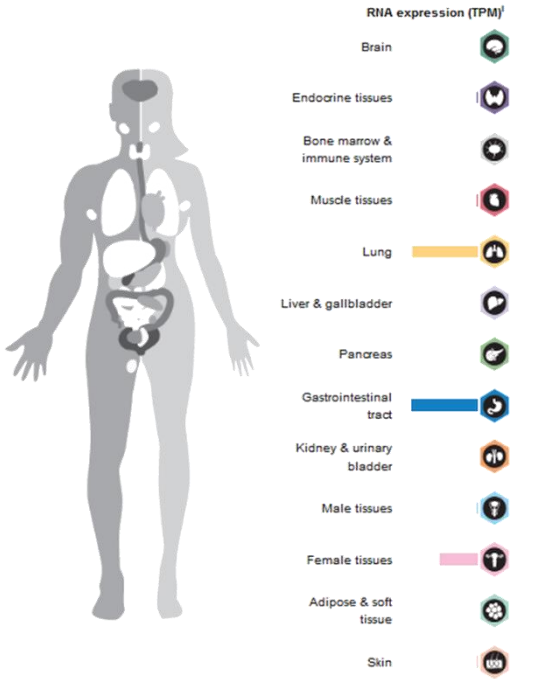

Figure 5. Expression profile of SLC6A4 in different tissues/organs in human. Data were taken from The Human Protein Atlas (http://www.proteinatlas.org) in December, 2018.

Thus, the membrane potential mediates the release of sodium and chloride molecules pre-bound to the 5-HTT protein and the 5-HTT protein passes into the cell. The 5-HTT protein releases serotonin in the cell and binds a potassium ion to itself. 5-HTT is activated by potassium ion and may be out of the cell. Serotonin (5-hydroxytryptamine; 5-HT) is an important neurotransmitter substance in the central and peripheral nervous system. After release of 5-HT into brain synapses, the Na^+ and Cl^- ions-dependent high-affinity serotonin transporter SLC6A4 (also called 5-hydroxytryptamine transporter, 5-HTT, SERT), which is localized in presynaptic neuronal membranes, effectively clears 5-HT from the synaptic space. Thus, the synaptic activity of 5-HT is terminated by 5-HTT and reintroduced into the neurotransmitter pool for re-use. In this way, 5-HTT has an important role in the retrieval of serotonin and the execution of serotonergic function (Gelernter J. Et al., 1998, Catalano M., 1999).

The 5-HTT activity is rapidly regulated by a number of G-protein-linked receptors and protein kinase-associated pathways including protein kinase C (PKC), PRKG1 (protein kinase G, PKG), and p38 mitogen-activated protein kinase (MAPK). The PKC-dependent phosphorylation and down-regulation of the 5-HTT protein is sensitive to extracellular 5-HT and plays a regulatory role in the transport of 5-HT (Ramamoorthy et al., 1998; Ramamoorthy et al., 1999; Zhu et al., 2004; Samuvel et al., 2005; Prasad et al., 2005).

Mutations

Most frequent mutations are located in the 5-HTTLPR of the promoter region of SLC6A4 gene. These mutations lead to the clinical picture of Autism (rs6365, rs28914832, rs140700) (Sutcliffe et al., 2005 ; Landaas et al., 2010 ; Adamsen et al., 2011), Increased rigid-compulsive behaviour in autism (rs28914833, rs28914834) (Sutcliffe et al., 2005; Rao et al., 2017), Obsessive-compulsive disorder (rs25532) (Wendland et al., 2007), Major depressive disorder (rs6354) (Rao et al., 2017), Panic disorder (rs3813034) (Gyawali et al., 2010), Unipolar disorder (Ogilvie et al., 1996), and Pulmonary arterial hypertension (Eddahibi et al., 2003) (Table 2).

Implicated in

The serotonin carrier protein encoded by SLC6A4 gene is the target of serotonin selective reuptake inhibitors, an important class of antidepressant drugs (Ramoz et al., 2006). Three alleles of 17-bp VNTR (variable number tandem repeat) were detected in the intron 2 region of the gene, between 9 (Stin2.9), 10 (Stin2.10), and 12 (Stin2.12) copies. Presence of Stin2.9 allele in humans has been reported to increase the risk of Major depressive disorder (MDD) (Ogilvie et al., 1996).

The 5-HTTLPR promoter sequence of the gene comprises two variant repeat length polymorphisms, known as the 16-element long (L) and 44-bp short (S) variant with 14 repetitive elements (Esterling et al., 1998; Sen et al., 2004). The L/L genotype from the 5-HTTLPR promoter variants causes more 5-HTT protein expression than the L/S or S/S variants (Canli and Lesch, 2007).

Analysis of lymphoblastoid cell lines with different genotypes revealed that the basal activity of the L variant of the SLC6A4 gene promoter was two times greater than that of the S variant (Lesch et al., 1996).

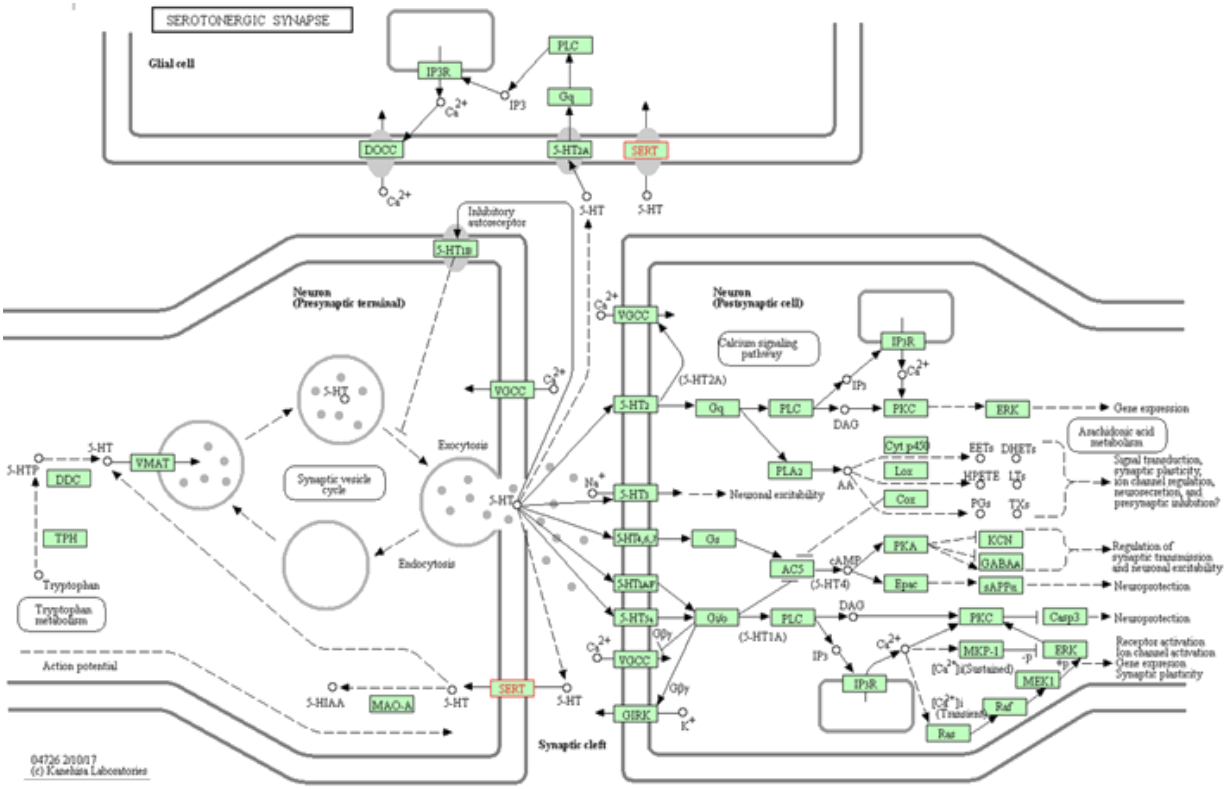

Figure 6. Serotonergic Synapse Pathway Map. Once released from presynaptic axonal terminals, 5-HT binds to receptors, which have been divided into 7 subfamilies on the basis of conserved structures and signalling mechanisms. These families include the ionotropic 5-HT3 receptors and G-protein-coupled 5-HT receptors, the 5-HT1 (Gi /Go -coupled), 5-HT2 (Gq-coupled), 5-HT4/6/7 (Gs-coupled) and 5-HT5 receptors. Presynaptically localized 5-HT1B receptors are thought to be the autoreceptors that suppress excess 5-HT release. 5-HT's actions are terminated by transporter- mediated reuptake into neurons, leading to catabolism by monoamine oxidase. Data were taken from KEGG: Kyoto Encyclopedia of Genes and Genomes (https://www.genome.jp/kegg/) in February, 2019.

Pairwise Alignment Scores

Gene		Identity (%)	
Species	Symbol	Protein	DNA
H.sapiens	**SLC6A4**		
vs. P.troglodytes	SLC6A4	99.4	99.3
vs. M.mulatta	SLC6A4	98.6	97.5
vs. C.lupus	SLC6A4	93.5	90.3
vs. B.taurus	SLC6A4	93.0	89.7
vs. M.musculus	Slc6a4	92.5	87.8
vs. R.norvegicus	Slc6a4	91.7	88.1
vs. G.gallus	SLC6A4	81.9	76.9
vs. X.tropicalis	LOC100493853	76.8	71.1
vs. D.rerio	slc6a4a	70.8	68.3

Figure 7. Pairwise alignment of SLC6A4 gene protein sequences (in distance from human) (HomoloGene, NCBI).

Missense/Nonsense Mutations					
#	**Location**	**Mutation**	**Protein**	**Reported Phenotype**	**Reference**
1	Exon 2	c.10A>G	p.T4A	Enhanced 5-HT transport activity	Parasad et al., 2005
2	Exon2	c.167G>C	p.G56A	Autism, association with	Sutcliffe et al., 2005
					Camarena et al., 2012
3	chr17:30218213	c.603G>C	p.K201N	Increased transporter activity	Rasmussen et al., 2009
4	Exon 4	c.643G>A	p.E215K	MAPK nonresponsiveness	Parasad et al., 2005
5	Exon 6	c.878C>T	p.S293F	Enhanced 5-HT transport activity	Parasad et al., 2005
6	Exon 7	c.1016C>T	p.P339L	Reduced uptake activity	Parasad et al., 2005
7	Exon 8	c.1084C>A	p.L362M	Enhanced 5-HT transport activity	Parasad et al.i 2005
8	Exon 9	c.1273A>C	p.I425L	Autism, association with	Sutcliffe et al., 2005
9	Exon 9	c.1273A>G	p.I425V	Obsessive-compulsive disorder,susceptibility, association	Ozaki et al., 2003
					Moya et al., 2013
10	Exon 10	c.1393T>C	p.F465L	Increased rigid-compulsive behavior in autism, association with	Sutcliffe et al., 2005
11	Exon 12	c.1648C>G	p.L550V	Increased rigid-compulsive behavior in autism, association with	Sutcliffe et al., 2005
					Rao et al., 2017
12	Exon13	c.1815A>C	p.K605N	MAPK nonresponsiveness	Parasad et al., 2005
					Rao et al., 2017
13	Exon 14	c.1861C>T	p.P621S	MAPK nonresponsiveness	Parasad et al., 2005
Splicing Mutation					
14	chr17:30216371	c.838-155G>A	NA	Autism, association with	Sutcliffe et al., 2005
					Landaas et al., 2010
Regulatory Mutation					
15	chr17:30237328	c.-1936G>A	NA	Obsessive-compulsive disorder, association with	Hu et al., 2006
					Perroud et al., 2010
					Hung et al., 2011
					Moya et al., 2013
					Stacey et al., 2013
16	chr17:30237152	c.-1760T>C	NA	Obsessive-compulsive disorder, association with	Wendland et al., 2008
					Fuxman Bass et al., 2015
17	chr17:30222880	c.-185A>C	NA	Major depressive disorder, association with	Rao et al., 2017
18	chr17:30197993	c.463T>G	NA	Increased expression	Vallender et al., 2008

					Seneviratne et al., 2009
19	chr17:30197786	c.670T>G	Na	Panic disorder, association with	Gyawali et al., 2010 Aoki et al., 2010 Hartley et al., 2012
Deletion					
20	Promoter	c.1212-1255 del TGCAGCC	NA	Anxiety related traits, association with	Helis et al., 1996 Marziniak et al., 2005 Borroni et al., 2006 Albani et al., 2009
	Location	**Repetition Sequence**	**Number Of Repetitions**	**Reported Disease/Phenotype**	**Referance**
21	Intron 2	(GGCTGYGACCYRGRRTG)n	10-12	Unipolar disorder, association with	Ogilvie et al., 1996
22	Intron 2	(GGCTGYGACCYRGRRTG)n	12	Pulmonary arterial hypertension, association with	Allen et al., 2008: Cao et al., 2009

Table 2. Solute Carrier Family 6 Member 4 (SLC6A4) related mutations.

In a later study, the expression of the native SLC6A4 gene in cultured lymphoblast cell lines from subjects with different SLC6A4 promoter genotypes was examined (Lesch et al., 1996).The mRNA concentration of the SLC6A4 gene in L/L cells was found to be 1.4 to 1.7-fold higher than the L/S and S/S cells (Lesch et al., 1996). Bradley et al. (2005) directly measured serotonin transporter mRNA levels and also identified 4 loci containing the serotonin transporter gene from 85 independent lymphoblast lines. They found strong impact of 5-HTTLPR on the mRNA exression (Bradley et al., 2005).

The Gly56Ala substitution in the exon 2 of the SLC6A4 gene has been reported to be associated with autism and exhibit structurally high SERT activity (Sutcliffe et al., 2005). I425V substitution in the exon 9 of the SLC6A4 gene has been reported to be associated with obsessive-compulsive disorder (OCD) (Ozaki et al., 2003; Kilic et al., 2003; Zhang et al., 2007). In addition, A-1438G and T102C polymorphisms were reported to be associated with OCD (Taylor, 2013; Taylor, 2016). Rao et al. (2017) reported that I550V (exon 12) and K605N (exon 13) substitutions of the SLC6A4 gene are associated with major depression disorder (MDD) and SA (non-fatal suicidal behavior) in addition to autism and OCD in 36 Chinese patients.

Animal Experiments

When 5-HTT was temporarily inhibited by fluoxetine (selective serotonin re-uptake inhibitor) in the early developmental period of mice, it was observed that adult mice exhibited abnormal emotional behaviors. It has been reported that serotonin plays a critical role in the maturation of brain systems that regulate emotional function, and that the low expression level of the SLC6A4 gene may be related to the development of psychiatric disorders in adults (Ansorge et al., 2004). A study of transgenic mice overexpressing the SLC6A4 gene and wild-type mice showed that right ventricular pressure was 3-fold higher in transgenic mice (Maclean et al., 2004). Page et al. (2009) reported macrocephaly in Pten +/- mice. Female Pten +/- mice had socialization disorder, whereas male Pten +/- mice had no socialization disorder. This phenotype was exacerbated in mice with Pten and SLC6A4 double haploinsufficiency. As a result of these findings PTEN and SLC6A4 genes have been reported to be associated with autism spectrum disorder (ASD).

Breast cancer

High expression is found in breast cancer, but the gene product is not prognostic according to The Human Protein Atlas.

A fusion gene PIP4K2B /SLC6A4 was found in breast cancer (Yoshida et al., 2013).

Obsessive-Compulsive Disorder (OCD)

Hu et al. (2006) found that the gain-of-function homozygous L(A)L(A) genotype was 2-fold in patients with OCD compared to healthy individuals. In a replication study in 175 trios consisting of probands with OCD and their parents, the L(A) allele was 2-fold overtransmitted to the patients with OCD. The HTTLPR L(A)L(A) genotype exerted 1.8-fold effect on risk of OCD, thus establishing the role of the HTT gene in OCD. In another study, the frequency of Stin2.12 allele in Asian patients with anxiety disorder (including OCD) was reported to be significantly higher compared to the healthy individuals (Ohara et al., 1998). There is also a possible association between OCD and Stin2.12 allele in Spanish Caucasian population (Baca-Garcia et al., 2007; Saiz et al., 2008).

Anxiety-Related Personality Traits

The homozygous or heterozygous form of the S-variant of the 5-HTTLPR polymorphism in the SLC6A4 gene has been reported to be associated with lower expression and openness, and higher neuroticism (Lesch et al., 1996). Individuals with 1-2 copies of the S-variant of the 5-HTTLPR polymorphism, which is implicated in reduced 5-HTT expression and function and increased fear and anxiety-related behaviours, demonstrated higher amygdala activity in response to fearful stimuli compared with individuals homozygous for the L-variant (Hariri et al., 2002). The altered function of the serotonin neurotransmission system causes aggressive behaviour in Alzheimer's patients (AD) (Brown et al., 1982; Palmer et al., 1988). In a study conducted on 137 AD patients, the aggressive behaviours (58 patients) were associated with L/L genotype (Sukonick et al., 2001).

Major Depressive Disorder (MDD)

People with L/S or S/S allele in stressful life conditions have been reported to have more depression and suicidal tendency than those with L/L allele (Caspi et al., 2003). They also reported that the individual's response to environmental insults was determined by environmental-gene interaction (Caspi et al., 2003). In a study conducted on Pomerania population, the relationship of S-variant with environmental interaction and depression was determined. The results of the study supported previous studies on the gene-environment interaction of the S allele. It has also been revealed to cause high mental vulnerability to social stress and chronic diseases (Grabe et al., 2005). Homozygous or heterozygous genotypes of the S-variant were associated with stress-related depression and anxiety disorders in elite athletes (Petito et al., 2016). The 5-HTTLPR polymorphisms of the SLC6A4 gene have been reported to be associated with prenatal and postnatal depression (Sanjuan et al., 2008; Oberlander et al., 2013). Interestingly, the genetic and epigenetic variations have been reported in the SLC6A4 gene of children exposed to prenatal depression (Devlin et al., 2010; Oppenheimer et al., 2013; Wankerl et al., 2014; Babineau et al., 2014; Green et al., 2017). 5-HTTLPR polymorphisms and DNA methylations of SLC6A4 gene have been reported to be associated with depression (Devlin et al., 2010; Sugawara et al., 2013).

Seasonal Affective Disorder (SAD)

Willeit et al. (2003) genotyped 284 subjects (138 SAD patients and 146 healthy individuals) to examine the relationship between L and S-variants in the 5-HTTLPR polymorphism of SLC6A4 gene with SAD. The distribution of genotype and S allele frequency was found similar between patients and healthy subjects, while they were correlated with the subtypes of DSM-IV depression. L allele was correlated with melancholic depression whereas S allele was related to atypical depression. It was concluded that 5-HTTLPR polymorphism affects the phenotypic disease expression but it is not the cause of disease.

The effects of light therapy on serotonin transporter binding (5-HTT BP_{ND}), which is biomarker of 5-HTT levels, in the anterior cingulate and prefrontal cortices (ACC and PFC) of healthy individuals during the fall and winter was studied. In winter, light therapy significantly decreased 5-HTT BP_{ND} by 12% in the ACC with respect to placebo, whereas in the fall, no significant change in 5-HTT BP_{ND} was measured. In this context, it has been reported that 5-HTT BP_{ND} can be used as a biomarker for the assessment of the modification effects of light therapy (Harrison et al., 2015). In a study on 20 SAD patients and 20 healthy participants the impact of seasonal (winter and summer) variations on 5-HTT activity was investigated by analysing brain 5-HTT BP_{ND} levels. The study reported a significant increase in 5-HTT BP_{ND} in different brain regions (including ACC and PFC) especially in severe SAD during winter. The 5-HTT BP_{ND} as biomarker in the diagnosis of SAD is important as it can be applied for the development of prevention strategies against disease progress (Tyrer et al., 2016).

Alcoholism

A meta-analysis study (data from 3,489 alcoholics and 2,325 controls) was conducted on the association of 5-HTTLPR polymorphisms of SLC6A4 with alcohol dependence. It has been reported that alcohol dependence complicated by a comorbid psychiatric condition or a more severe form of alcoholism is associated with the S-variant (Feinn et al., 2005). In a study conducted on university students, the S-variant was reported to be associated with high alcohol consumption (Herman et al., 2003). High

alcohol consumption in men with homozygous or heterozygote genotypes of the S-variant has been reported, whereas it was seen only in the heterozygous women (Munaf et al., 2005). In a study conducted on 273 (78.5% male) alcoholic individuals of the Caucasus and Hispanic origin, it was reported that G allele carriers for the rs1042173 SNP in the 3'UTR region of the SLC6A4 gene had lower alcohol consumption than T-allele homozygotes (Seneviratne et al., 2009). G allele transfection to HeLa cells resulted in higher mRNA and protein expression compared to T allele transfected cells (Seneviratne et al., 2009).

Sudden Infant Death Syndrome (SIDS)

L/L genotype and excess of L-variant have been reported to be associated with SIDS (Narita et al., 2001; Weese-Mayer et al., 2003). In addition, the Stin2.12 allele has been associated with SIDS in African-Americans and Japanese, whereas it is not associated with SIDS in Caucasian-Americans (Narita et al., 2001; Weese-Mayer et al., 2003).

Panic Disorder (PD)

The rs3813034 variant in the 3'UTR region of the SLC6A4 gene has been reported to be related to PD (Gyawali et al., 2010). Decreased SLC6A4 gene expression due to the gene polymorphisms in midbrain, hypothalamus and temporal lobe has been associated with PD (Maron et al., 2006). Strug et al. (2010) reported that rs140701 variant of the SLC6A4 gene may be associated with PD.

Bipolar Affective Disorder (BPAD) or Manic-Depressive Illness (MDI)

The disorder of the neurotransmitter system, including serotonin and monoamines, has been reported to be associated with bipolar disorder (Scott et al., 1979; Kapur and Remington, 1992). The patients with BPAD without panic disorder exhibited statistically higher frequencies of the Catechol O-Methyltransferase (COMT) Met158 and the S-variant 5-HTTLPR genotypes with respect to healthy individuals (Rotondo et al., 2002). When the relationship between L and S-variant polymorphisms of SLC6A4 gene and BPAD and unipolar depression were investigated by meta-analysis study, it was revealed that the S-variant could be associated with BPAD but not with unipolar depression. The L-variant was not implicated in BPAD and/or unipolar depression (Lasky-Su et al., 2005). However other studies reported no significant relationship between SLC6A4 5-HTTLPR and VNTR polymorphisms and BPAD (Mendlewicz et al., 2004; Cho et al., 2005). The association between epigenetic variations of SLC6A4 gene and BPAD were studied on 20 bipolar monozygotic twins with respect to 20 healthy subjects. The promoter-wide DNA methylation analysis of lymphoblastic cell lines (LCLs) revealed DNA hypermethylation in SLC6A4 gene that can be an epigenetic mark resulting from a G×E interaction leading to the development of BPED (Sugawara et al., 2011). In a study on the association of SLC6A4 and DRD2 (dopamine D2 receptor) genes with BPED, the gender specific differences in SLC6A4 gene polymorphisms were reported. The results revealed gender-specific association of the DRD2 A1/A1 and the 5-HTTLPR S/S, S/LG, and LG/LG (S+) genotypes in type I and type II men, but not in women. A significant interaction for the DRD2 A1/A1 and 5-HTTLPR S+ polymorphisms was also found only in type I and type II men (Wang et al., 2014).

Pulmonary Hypertension (PPH)

Smooth muscle cells (SMC) of pulmonary artery in PPH patients grow faster than controls when 5-HTT expression is stimulated by serotonin. As a result of these findings, 5-HTT has been shown to play a key role in the pathogenesis of SMC proliferation and 5-HTT polymorphisms are associated with PHH (Eddahibi et al., 2001). The higher 5-HTT expression was reported in pulmonary artery SMC in patients with L/L genotypes compared to L/S and S/S genotypes, resulting in more severe PPH. (Eddahibi et al., 2003). In a study on the association of idiopathic PPH with 5-HTT polymorphism in children, the L/L genotype has been reported to be associated with the aetiology of PPH (Vachharajani and Saunders, 2005).

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